REMARKS

The official action of 29 May 2008 has been carefully considered and reconsideration of the application as amended is respectfully requested.

Claim 12 has been amended in accordance with the description in the specification as filed at, for example, Example 12 on page 16 and Fig. 9 of the drawings (see discussion below). Claim 14 has been amended in accordance with the description in the specification as filed at, for example, Example 11 on pages 15-16 and Fig. 8 of the drawings (see discussion below).

New claims 34-36 have been added based on the description in the specification as filed at, for example, page 1, line 22 to page 2, line 2 and page 6, lines 20-31. In particular, the specification conveys to one of skill in the art that the claimed method addresses the problems with the prior art hepatoprotective agents described in the specification at page 1, lines 28-35, which include administration of hepatoprotective agents in different cases, including extreme cases wherein the hepatoprotective agent is used to improve the survival of an individual. The specification reasonably conveys to those of skill in the art that the claimed composition can provide an improvement in each of the different cases, including the extreme case that threatens the survival of a subject.

New claims 37-38 have been added based on the description in the specification as filed at, for example, pages 14-15 and Figs. 6A-C (see discussion

below).

The dependency of claim 32 has been amended to remove the basis for the objection to this claim.

Claims 12-18 and 28-33 remain rejected under the enablement requirement of 35 USC 112, first paragraph. Applicants respectfully traverse this rejection.

First, Applicants respectfully note that the scope of the claims has been limited to the administration of the claimed cardiotrophin to counter the effects of a loss of functional liver cells by stimulating DNA in hepatocytes or by proliferation or differentiation of the hepatocytes (claim 12 and dependent claims) or to exert an antiapoptotic effect (claim 14 and dependent claims). Although the dependent claims recite that the subjects to which the cardiotrophin is administered suffer from particular liver diseases, these recitations only limit the subject populations to whom the cardiotrophin is administered. The recitations do not increase the scope of the claims and do not alter the fact that all claims are directed to (a) the stimulation of DNA in hepatocytes or proliferation and differentiation of hepatocytes or (b) to exerting an antiapoptotic effect, and not to curing any particular disease. Under these circumstances, the claims must be evaluated to determine whether the specification enables the claimed effects and not whether the specification enables curing of the disease. See MPEP 2107.03(VI) ("Only those claims for which an asserted utility is not credible should be rejected. In such cases, the Office should carefully review what is being claimed by the applicant. An assertion that the claimed invention is useful in

treating a symptom of an incurable disease may be considered credible by a person of ordinary skill in the art on the basis of a fairly modest amount of evidence or support. In contrast, an assertion that the claimed invention will be useful in "curing" the disease may require a significantly greater amount of evidentiary support to be considered credible by a person of ordinary skill in the art. ").

With particular respect to claims 35-37, Applicants respectfully note that these claims are *a fortiori* enabled because the subjects do not have a life threatening disease.

With particular respect to claims 16-17 and 38-39, even assuming for the sake of argument that these claims were construed as treatment of a life-threatening disease itself, such as alcoholic hepatitis or cirrhosis, Applicants respectfully submit that the specification enables such treatment. (Note: treatment is different than cure, see above.) Thus, Fig. 6 provides a graphical representation of the serum levels of transaminases and histologic images of hepatic tissue from three models of induction of fulminant hepatitis in mice. As discussed in the specification at pages 14-15, one group of mice were treated with Ad-CT-1 48 hours prior to the induction of hepatitis whereas another (control) group was not. As described in page 15 third paragraph of the specification, Fig 6C shows a marked decrease in the figure for transaminases and in the number of apoptotic hepatocytes in the mice treated with AdCT-1 compared with the mice control. The level of transaminases is a well known parameter for diagnosis of liver damage, particularly for hepatitis, but also of other liver diseases, such as cirrhosis. These results show that the claimed method is effective for treating liver diseases, such as hepatitis, that are mediated by increased levels of transaminases.

In maintaining the enablement rejection, the Examiner has drawn a distinction between the administration of Ad-CT1 on the one hand and the administration of CT-1 as a recombinant protein on the other, and appears to contend that evidence showing enablement as to the former is not evidence of enablement as to the latter. Applicants respectfully disagree and note that one of skill in the art would recognize a reasonable correlation between the effectiveness of administering Ad-CT1 on the one hand and administering Ad-CT-1 as a recombinant protein on the other. This is all that is required for the evidence to be probative. See MPEP 2107.03 ("As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility.").

Moreover, the application provides examples demonstrating the effectiveness of both Ad-CT1 and CT-1 without drawing any distinction between them because one of skill in the art would recognize a correlation between the two. Thus, some of the working examples refer to the effect of Ad-CT1 on hepatic regeneration after partial/extended hepatectomy (examples 8.2 and 9), and the protective effect of Ad-CT1 against apoptosis/necrosis of hepatocytes (example 10), while Example 11 demonstrates that CT-1 (recombinant protein) was able to cause a marked delay in the start of apoptosis and confirms that CT-1 as recombinant protein is capable of exerting such antiapoptotic effect. Example 12 shows that CT-1 as recombinant protein is able to induce DNA synthesis in hepatocytes. Example 13 shows that CT-1 as recombinant protein is capable of inducing the JAK/STAT signalling pathway as well as the PI-3K/AKT survival pathway. The cascade of signals induced by CT-1 in hepatocytes

explains how CT-1 as recombinant protein acts as a cytokine with antiapoptotic effects via the PI-3k/AKT pathway and as an inducer of proliferation and differentiation in hepatocytes via the JAK/STAT-3 pathway.

In short, Applicants respectfully submit that, when considered as a whole, the evidence in the present case, including the evidence in the specification discussed above and in the Declaration of Dr. Jesus Prieto Valtuena discussed in Applicants' response filed 7 March 2008, leads to the conclusion that the specification is enabling for the invention as now claimed. With respect to the Valtuena Declaration, the Examiner did not fully consider the same because one of the publications referred to therein, WO95/29237, was not made of record. Applicants submit herewith an Information Disclosure Statement to make this publication of record.

In view of the above, Applicants respectfully submit that all rejections and objections of record have been overcome and that the application is now in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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